Chapter 7

General Discussion


Chapter 7 – General discussion

In this chapter, the main results of this thesis are discussed and suggestions for future research are given. The aim of the thesis was to study the hypothesized model (Figure 1). Results of this thesis brought evidence to confirm some of the pathways depicted in the study model.

First, we confirmed that wearing a soft brace reduces activity limitations in persons with knee osteoarthritis (OA). In Chapter 2, we presented a systematic review with meta-analyses indicating that wearing a soft brace results in small to moderate effects on self-reported physical function (i.e., activity limitations) in the long term in comparison to persons receiving standard care without a soft brace. Because of lack of studies, we were not able to synthesize data on performance-based physical function. The results of the review are in agreement with a previous systematic review on this topic. In comparison review, we conducted meta-analysis which provided higher-quality evidence. Each meta-analysis included from two to three studies with low methodological quality. We concluded that high-quality studies investigating the efficacy of soft braces in knee OA are warranted to improve confidence in the findings.

We decided to conduct a laboratory trial to determine the immediate efficacy of a soft knee brace on activity limitations in persons with knee OA. In Chapter 4, we reported that wearing a soft brace significantly reduced time to complete both the 10-meter walk test and the Get Up and Go (GUG) test by 0.23 s (95% CI: -0.31 -0.13 and -0.38 -0.07, respectively), compared to not wearing the brace. A similar improvement was observed in a previous study evaluating the effect of wearing a soft brace on activity limitations, assessed with performance-based tests. Our findings confirm that wearing a soft knee brace allows persons with knee OA to walk faster. Studies providing information on the minimal clinically important change of the 10-meter walk test and the GUG test are necessary to conclude the clinical relevance of the effects we found.

Second, we confirmed that wearing a soft knee brace reduces pain in persons with knee OA. In Chapter 2, the systematic review with meta-analysis showed that wearing a soft knee brace results in moderate effects on pain in the immediate and long term. In line with the results from the systematic review, in Chapter 4, results from our own laboratory trial showed that wearing a soft brace reduced pain in the immediate term. We observed a 0.6 (95% CI: 0.97 -0.23) and 0.8 (95% CI: -1.11 -0.43) points decrease of pain on the Numeric Rating Scale (NRS) for level and perturbed walking, respectively. This effect is close to the one-point threshold for the minimal clinically important difference for NRS pain in clinical trials. The results are in agreement with previous studies in which, Bryk et al. observed a 0.6 mm reduction in the Visual Analog Scale (VAS) for pain during Stair Climb Power Test (SCPT), while Schween et al. and Hassan et al. reported a similar decrease in VAS for pain during level walking.

Third, we confirmed that wearing a soft knee brace reduces knee instability in persons with knee OA. In Chapter 4, it was shown that a soft brace reduced self-reported knee instability in persons with knee OA. These results are in agreement with a previous report on this subject. We also showed that wearing the brace improved confidence in the knees, which to our knowledge, is the first report on that subject. Additional novelty of our study was to evaluate the effect of a soft knee brace on self-reported knee instability and knee confidence during walking with external perturbations on the treadmill. External perturbations provide a more stimulating and challenging environment for knee stability, and simulate situations in which persons with knee OA might experience increased perception of knee instability. Knee OA could affect the ability of the neuromuscular system to execute appropriate commands in response to external challenges, resulting in joint instability. It is therefore important to show that, even when participants were subjected to external perturbations, the effect of wearing a soft brace on self-reported knee instability and confidence in the knees continued.

Although the effect of a soft knee brace on self-reported knee instability is important, it might be subject to bias. Therefore, in Chapter 5, we evaluated the effect of a soft knee brace on objectively assessed, dynamic knee instability. Dynamic knee instability was expressed by the Perturbation Response (PR), a measure reflecting deviation in the mean varus-valgus angle during walking while a controlled mechanical perturbation was applied, with respect to level walking. It was demonstrated that...
wearing the brace significantly reduced dynamic knee instability compared with not wearing a brace. These results indicate that wearing a soft brace results in an objective improvement of knee instability, beyond subjectively reported improvement.

Fourth, we did not confirm that wearing a soft knee brace improves proprioception. In Chapter 6, we reported that wearing the soft knee brace did not have an effect on proprioception and that proprioception did not mediate the effect of wearing a soft knee brace on decrease of activity limitations in persons with knee OA. This is in contrast to suggestions from the literature. A likely explanation is that proprioception was not measured while wearing the brace, but following exposure to wearing a brace. Although it has been shown that stimulation of cutaneous mechanoreceptors has effects lasting until one hour, stimulation from the brace may not have been strong enough to induce lasting effects. Future studies assessing proprioception while wearing a soft knee brace are required to determine if proprioception plays a mediating role in soft brace-induced effects in persons with knee OA.

Finally, in Chapter 6, we confirmed that decrease of pain and reduction of dynamic knee instability, but not an improvement in proprioception, are pathways via which wearing a soft knee brace decreases activity limitations in persons with knee OA.

Reduction of pain accounted for 43% and 44% decrease of time to complete the 10-meter walk test and the GUG test, respectively. This effect can be explained by the tactile stimulation of the knee skin provided by a soft brace. Such stimulation may cause neural inhibition, facilitating the entry of impulses through the large afferent nerve fibers. Consequently, such stimulation may lead to reduction in transmission of pain signals. Self-reported limitations in activities in persons with knee OA are largely dependent on pain; therefore it seems that the application of a soft brace results in less pain which then leads to walking at a higher speed. We did not find evidence that pain, as assessed by the pressure pain threshold (PPT) test, mediated the effect of wearing a brace on activity limitations. A likely explanation could be that for practical reasons PPT was not measured while wearing a brace but after wearing a brace.

Reduction of objectively measured dynamic knee instability accounted for 13% and 26% decrease of time to complete the 10-meter walk test and the GUG test respectively, while wearing a brace. It has been suggested that the tactile stimuli provided by a soft brace contribute to the signaling of limb movements to the brain which processes these sensory inputs to create perceptual representations of limb movements. Primary sensorimotor cortex activity has been shown to be influenced by peripheral sensory input to the knee joint by means of a soft brace. It is therefore plausible that the central nervous system uses this additional sensory information to elaborate on descending motor strategies (i.e. improved muscle activity), resulting in enhanced knee joint stability. It is likely that improved instability, i.e. limiting excessive joint movement, will translate into an ability to walk faster.

Development of the study model
The thesis brought new hypotheses that served to further develop the study model (Figure 2). Solid black lines indicate the paths that were confirmed with the results of this thesis; dotted black lines indicate the hypothesized paths that need to be evaluated in future studies.

We speculate that the path between decrease of dynamic knee instability and reduction of activity limitations might be mediated by increase in confidence in the knee. This thesis did not provide evidence explaining how wearing a brace resulted in reduction in dynamic knee instability and reduction in pain. We hypothesize that there are several factors influencing the paths between wearing a soft brace and reduction in pain and in dynamic knee instability. We believe these factors can act as additional mediators and/or as moderators of these relationships (Figure 2). Moderation occurs when the relationship between two variables depends on the level of a third variable (i.e. moderating variable). In that regards, we suggest that the effect of wearing a soft brace on decrease in pain might be mediated by the neurophysiological effects, such as an increase of skin temperature or...
neural inhibition. The effect of wearing a soft brace on decrease of dynamic knee instability might be explained by an additional sensory input via stimulation of skin mechanoreceptors, adding to improvement in proprioception. However, it is likely that this additional sensory input will be greater in persons with knee OA who have low skin sensitivity, i.e. have decreased ability to detect light touch on the skin. In these people, additional sensory input, for example by means of a soft knee brace, might further add to improvements in an ability to detect joint motion and position. For this reason, skin sensitivity might serve as a moderator of the effect of a soft knee brace on proprioception. Furthermore, the effect of enhanced proprioception on dynamic knee instability might be greater in persons with knee OA who are unable to fully activate their knee muscles or are unable to activate them in the right time (i.e. delayed muscle response). Activity of quadriceps and hamstring muscles is one of the key determinants of dynamic knee stability. It is plausible that the central nervous system uses the additional sensory information, by means of a soft knee brace, to elaborate descending motor strategies, resulting in increased / enhanced activity of the knee muscles that limits knee movements in response to perturbations. Thus, muscle activity may act as a moderator of the beneficial effect of improvement of proprioception on reduction of dynamic knee instability.

To study the hypothesized model, future studies should account for the suggested mediators and moderators and implement another statistical methods to test it, such as moderated-mediation analysis. This model might enhance the understanding of the effects of soft knee braces and serve as a hypothesized study model for future research in persons with knee OA.

Comparison between a non-tight and a tight brace

Another aim of the thesis was to compare the effects between a non-tight and a tight soft knee brace. We hypothesized that a non-tight brace would elicit stronger effects than a tight brace. This hypothesis was based on a study reporting that a non-tight brace reduced pain and improved postural sway while a tight brace did not. Authors speculated that a non-tight brace provided more recurrent stimuli, by allowing movement between the brace and the skin, and thus elicited continuous response from cutaneous receptors, adding to improvements in proprioception and subsequently to reduced activity limitations and knee instability. By contrast, a tight brace might provide constant pressure, to which skin mechanoreceptors quickly adapt.

In Chapter 4 we showed that there was no difference in outcome measures between a non-tight and a tight soft brace, with an exception of the effect on the 10-m walk test. In Chapter 5, we showed that there was no difference between a non-tight and a tight brace in reduction of dynamic knee instability. Hassan et al. used a tubigrip elastic bandage, whereas we used a soft brace specifically designed for the knee joint. We are therefore unaware whether the level of pressure exerted on the skin by our soft brace was comparable to that used by Hassan et al. Studies with a reliable and valid measure of tightness, for instance by means of pressure sensors, are warranted, to determine whether certain levels of tightness of a soft brace are of influence on clinical outcomes.

Dynamic knee instability: need for additional objective parameters

In chapter 5, we evaluated the effect of wearing a soft knee brace on dynamic knee instability. An objective measure of dynamic knee instability was the PR, a biomechanics-based measure reflecting a deviation in the mean varus-valgus angle after a controlled mechanical perturbation, in respect to level walking. We selected deviation in the mean varus-valgus angle as the reflection of dynamic knee instability. However, dynamic knee instability might also be reflected by other parameters, i.e. sagittal and/or transverse plane movement, muscle activity and spatio-temporal parameters.

Biomechanics of the knee joint involve movement within three planes: frontal (varus-valgus angle), sagittal (flexion-extension angle) and transverse plane (external -internal rotation). It has been shown that persons with self-reported knee instability show different patterns during walking in the sagittal and transverse planes than persons with knee OA and without episodes of knee buckling or giving-way. For this reason, future studies that intend to use the PR as a measure of dynamic knee instability might also account for deviations in the transverse and sagittal planes.

Quadriceps and hamstring muscles are considered principal active stabilizers of the knee joint. The two main factors that determine the muscle’s function are muscle strength (usually tested with torque generation capability) and muscle activation that reflects the ability of the nervous system to activate the muscle (usually measured with EMG), with the latter contributing to the first. It has been previously shown that lower muscle strength was significantly associated with the presence of self-reported knee instability in persons with knee OA. In addition, previous research has shown that persons with knee OA showed adaptation in muscle activity around the knee joint in response to external perturbations. The role of muscle function in
However, because the knee OA population is heterogeneous, soft knee bracing may need to be tailored to specific homogenous phenotypes of persons with knee OA, to optimize its overall efficacy. Future work should evaluate the effects of wearing a soft knee brace in different phenotypes of persons with knee OA.

Based on the results from Chapter 3, persons with knee OA and inflammatory response might present one of knee OA phenotype 37,38 where use of soft knee braces could be applicable. In Chapter 3, it was reported that proprioception mediates the association between systemic inflammation and muscle weakness in persons with knee OA. The mediation by poor proprioception can be explained by abnormal neural afferent discharges of mechanoreceptors. As a result of systemic inflammation, $\gamma$-motor neuron excitability could be decreased and lead to arthrogenic reflex inhibition 39. The change in physiological properties of mechanoreceptors by inflammation could be a pathway through which systemic inflammation affects muscle strength. The mediated effect of proprioception on the association between systemic inflammation and muscle weakness was 1.8% 40. Theoretically, improving proprioception, for instance by means of a soft brace, might contribute to better outcome in rehabilitation, adding to the improvements in muscle strength and thus decrease in activity limitations. Nevertheless, longitudinal data are needed in order to determine the clinical significance of the observed effect.

**Main conclusions**

In summary, the following conclusions can be drawn from this thesis:

- Wearing a soft knee brace is efficacious in reducing pain and activity limitations in the immediate and long term in persons with knee OA.
- Wearing a soft knee brace is efficacious in improving several knee function-related parameters (knee instability and knee confidence) that might generalize to daily life of persons with knee OA.
- The beneficial effect of wearing a soft knee brace on activity limitations are driven by reduction of pain and dynamic knee instability.
- Independent from whether a soft brace is tight or less tight, the effects of clinical outcomes are similar.
Directions for future research
Based on the study findings in this thesis, the following directions for future research are suggested:

• Studies evaluating the effects of soft bracing on pain and activity limitations in daily life of persons with knee OA are needed to strengthen the evidence supporting the use of soft knee braces.

• To provide a more accurate objective assessment of dynamic knee instability, future studies should account for additional objective determinants of dynamic knee instability.

• Future studies are needed to study the developed study model and to determine mechanisms underlying the beneficial effects of a soft knee brace on pain and dynamic knee instability.

• Additional studies are required to explore the role of proprioception in soft brace-induced effects in persons with knee OA.

• To determine whether certain levels of tightness of a soft knee brace are of influence on clinical outcomes, a valid and reliable measure of tightness is necessary.

• Future studies should evaluate whether a soft knee brace made of materials retaining heat and whether combing electrical stimulation with a soft knee brace has added benefit to reduction of pain and dynamic knee instability.

• Given that treatment of knee OA should be personalized, effects of soft knee bracing shall be evaluated in different clinical OA phenotypes.

Reference List


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